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Rifampicin-Induced Toxicity and the Ameliorative Potential of *Cynodon dactylon*: A Comprehensive Review

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A B S T R A C T

Rifampicin is one of the primary agents used in the treatment of tuberculosis, as it remains an important component of tuberculosis prevention as well as treatment of other bacterial infections. However, besides its therapeutic roles, it also poses a threat of negative side effects, among which liver toxicity is the most prominent one. Mechanisms of rifampicin toxicity imply that its toxicity has several components, which might be either related to the disturbance of processes associated with the metabolism of foreign substances, activation of pregnane X receptor pathways, manifestation of oxidative stress and free radicals creation, as well as lipid peroxidation process, activation of the processes caused by reports of the endoplasmic reticulum, disabling of bile acids transport, lipid accumulation in the liver cells, inflammation activation in the organism and introduction of unusual ways of cells' programmed death. All these processes might lead to the situations like liver malfunctioning, the release of certain enzymes into the blood, bilirubinism and symptoms of diseases. Studies conducted on animals show the presence of renal and systemic problems due to the action of the active components over a lengthy period of time. *Cynodon dactylon* (L.) Pers is a plant that has been used in traditional medicine. The data received from technical studies show that that it is made of phenols, flavonoids, carotenoids, alkaloids and glycosides, etc. The extracts obtained from this plant were shown to have the abilities to mitigate oxidative stress, provide antioxidant properties and prevent harm to the liver caused by other toxic substances. The aqueous extracts showed lower activities of serum transaminases and alkaline phosphatases and improved liver structure in rats exposed to paracetamol toxicity. Some synthetic diets with the extract are known to be effective in treatment of hepatic damage due to streptozotocin use. However, the evidence of what influence, if any, the Cynodon plant has on the activity of rifampicin is not enough. The objective of this review is to summarize the available in literature information on liver inflammation risk with rifampicin use and the potential of *C. dactylon* in preventing the consequences of this process. The reviewed aspects include the causes of liver impairment with rifampicin, oxidative processes in the human body, heats of the liver damage, composition of the plant, evidence of its protective action and mechanisms of such action.

Introduction

Tuberculosis (TB) still remains a potent infectious disease and a combination of drugs is usually required for curing it. One of the significant drugs used during TB treatment is rifampicin which is known to effectively treat the disease (Shehu *et al*., 2016). The principal action of rifampicin is that because of its ability to inhibit bacterial DNAD-dependent RNA polymerase it is widely used combined with other drugs like isoniazid, pyrazinamide, and ethambutol (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK], 2018). Nevertheless, the drug has positive traits that help it interact with several hepatic metabolic enzymes and transports. Thus, it works as a strong inducer of pregnane X receptor (PXR), which is a nuclear receptor that takes the responsibility for the regulation of genes taking part in the metabolism and transport of xenobiotics (Chen & Raymond, 2006; Shehu *et al*., 2016). Therefore, the activation of rifampicin PXR results in the induction of the drug enzymes and transports in particular CYP34 and P-glycoprotein, which is the reason rifampicin possesses effects on other drugs (Chen & Raymond, 2006; Shehu *et al*., 2016).

Liver is one of the most significant organs in terms of drug metabolism and detoxification, as hepatocytes contain many enzyme systems responsible for drug metabolism and elimination. According to research, enzymes defined as phase I enzymes and cytochrome ombre and transporters play important roles in the drug metabolism process at the level of the liver. In addition, it is possible to state that some drugs can influence these processes leading to disorder of cellular metabolism (for instance, redox balance and lipid metabolism) and contribute to the disruption of metabolic processes occurring in liver cells. Rifampicin is the drug that is processed in the liver and interacts with a variety of enzymes there. These facts lead to numerous drug interactions and liver problems (NIDDK, 2018; Wang *et al*., 2014). Although infection is considered to contribute to drug-induced liver damage, evidence shows that there have been extremely few pure cases of rifampicin-induced liver damage. Long-term use of rifampicin may result in the development of minor, transient increases in serum activity of aminotransferases in about 10-20% of cases. At the same time, a variety of changes in bilirubin concentration may be noticed due to the influence of rifampicin on its concentration in the liver (NIDDK, 2018). Very rarely, rifampicin can result in drugs-induced liver injury manifesting cholestatic, hepatocellular, or mixed type of damage that may lead to severe liver damage and jaundice (NIDDK, 2018). It should be noted that liver damage can increase if rifampicin is taken together with other hepatotoxic drugs – isoniazid

and pyrazinamide (Wang *et al*., 2014). The development of liver injury caused by antituberculous medication varies from one patient to another as it is determined by multiple patient-related and medication-related factors.A number of factors can affect the incidence and severity of the liver injuries caused by antituberculosis drugs. There are a number of such determinants including older age, nutritional status and malnutrition, consumption of alcohol, chronic liver diseases, viral hepatitis, pre-existing liver problems, variability of genotypes and metabolic capabilities (Shakya *et al*., 2004; Saukkonen *et al*., 2006). Pre-existing liver problems can be regarded as the major determinants of the liver injury since patients with lower liver capacity are more likely to suffer severe consequences of drug-related liver injury. In addition, recent clinical studies show that malnutrition and other patient-specific factors influence the development of drug-induced liver injury. The having clear ideas about the biochemical and histopathological processes caused by rifampicin as well as the elaboration of the measures aimed at decreasing liver toxicity are of great significance for researchers and clinicians.

The mechanism of the drug has evolved over the time and in the past it was regarded that the main mechanisms of action were connected to oxidative damage and the leakage of the enzymes from hepatocytes, while now it has been established that the action of rifampicin takes place via a more intricate pathway involving more components including:

PXR, CYP3A family of enzymes, transporters of bile acids, FXR, endoplasmic reticulum stress, lipid accumulation, inflammatory macrophages, malfunctions of the autophagy process and other forms of programmed cell death. The study by Zhuang *et al*. (2022) performed the analysis of rifampicin- and isoniazid-induced liver injuries concentrating on the following aspects: cholestasis, endoplasmic reticulum stress, lipid accumulation and the like being the core aspects of the hepatotoxicity of rifampicin.As noted by Ezhilarasan (2023), oxidative stress along with inflammation, apoptosis, cholestasis, and dyslipidemia play a fundamental role in the above-mentioned phenomenon. This information has recently received support from new studies. Then, as the impact of oxidative stress and inflammation can be altered, a number of studies seek to use plant-based substances and phytochemicals to increase the function and structure of the liver. The effect of natural products on the protection of liver can involve a number of processes which include several mechanisms, i.e., radicals scavenging with antioxidants as part of natural substances, regulation of oxidant signaling in cells, control of the action of inflammatory factors, maintenance of the membrane integrity, and regulation of the metabolism and cellular stress processes (Madrigal-Santillán *et al*., 2014; Li *et al*., 2015). This allows applying natural products in the case of chemically-induced liver injury connected with oxidative stress and mitochondrial dysfunction. In search of which plants or natural substances can prevent liver damage, scientists have examined several classes of active components, including flavonoids, particularly quercetin recognized for its antioxidant and anti-inflammatory properties (Li *et al*., 2016).Other phytochemicals such as phenolic compounds (namely gallic and rosmarinic acids) are known to help in reducing free radical concentration in the body, representing additional anti-inflammatory activity and constraining lipid peroxidation. Specifically, phenolic compounds like resveratrol are known to mitigate oxidative stress, claim functions related to mitochondria, and facilitate apoptosis (Bishayee *et al*., 2010). Also, curcumin is singled out as the most significant phenolic compound, making people interested in studying its antioxidant and anti-inflammatory properties. Moreover, silymarin serves as a bioactive compound extracted from Silybum marianum, which is abundant in flavonolignans and therefore is one of the most studied herbal hepatoprotective substances, possessing antioxidant and anti-inflammatory effects (Abenavoli *et al*., 2018). Nonetheless, despite the wide-ranging positive theoretical implications, natural plants and crude herbal medications face a multitude of biological and chemical challenges. The reason for this lies in the fact that, unlike isolated substances, extracts of plants consist of a great number of phytocompounds with various possible additive or synergistic effects on numerous molecular targets. Thus, this knowledge can be beneficial in combating complex pathological processes such as oxidative and inflammatory liver damage (Ekor, 2014). At the same time, this very complexity is the reason for many difficulties in replicating experiments. Specifically, when it comes to quality control, the quality of substance highly depends on geographical location, environmental conditions, vegetation season, a part of the plant chosen for preparation, and extraction techniques. This understanding forces researchers to find ways to standardize the quality of a crude plant extract and determine its constituents and dosage as well as toxicity level (Ekor, 2014; Kunle *et al*., 2012). As for *Cynodon dactylon*, it is a perennial weed that belongs to the Poaceae family and is popular throughout the world including India, where it can be called Durva or Doob. According to Ashokkumar *et al*. (2013) and Shendye and Gurav (2014), this plant has a rich ethnomedicinal history and is connected with a number of traditional medicinal applications. In their previous works, the authors presented the traditional uses of the plant and obtained the phytochemical composition of the extract that was shown to contain flavonoids, carotenoids, alkaloids, glycosides, triterpenes, phenolic compounds, etc. Therefore, various studies were conducted in order to explore the antioxidant properties of the *C. dactylon* extract and identify its hepatoprotection abilities. The basis for the interest in *C. dactylon* in terms of rifampicin intoxication can be understood from two perspectives. First of all, the components of rifampicin damage include oxidative, inflammatory, constructive, and metabolic processes among others. Second, there is some evidence that *C. dactylon* may possess antioxidant and hepatoprotective properties under various conditions. However, the fact that there is no evidence confirming the efficiency of a product created from *C. dactylon* leaves against rifampicin toxicity should also be taken into consideration.

Table 1. Key pharmacological and toxicological features of rifampicin

Feature	Summary	Relevance
Primary use	First-line antitubercular drug	Essential but long-course therapy increases importance of adverse-event monitoring
Major molecular target	Bacterial DNA-dependent RNA polymerase	Explains bactericidal action
Key host interaction	PXR and drug-metabolizing enzymes/transporters	Drives drug interactions and contributes to metabolic disturbance
Principal toxicity focus	Liver injury	Can be hepatocellular, cholestatic or mixed
Mechanisms	Oxidative stress, ER stress, cholestasis, lipid dysregulation, inflammation	Provides targets for protective interventions
Common biomarkers	ALT, AST, ALP, bilirubin, MDA, GSH, SOD, CAT	Useful for experimental evaluation

Table 2 Phytochemical groups of *C. dactylon* and relevance to hepatoprotection

Group	Examples/description	Potential relevance
Flavonoids	Apigenin, luteolin, vitexin reported in reviews	Antioxidant and anti-inflammatory signaling
Phenolics	Phenolic acids and related compounds	Radical scavenging and lipid-peroxidation control
Terpenoid-related compounds	Triterpenoid/terpenoid classes	Possible membrane and inflammatory effects
Carotenoids	Reported in pharmacognostic reviews	Antioxidant capacity
Fatty-acid derivatives and phytol	Detected in GC-MS studies	May contribute to extract bioactivity; role requires clarification
Alkaloids/glycosides/saponins	Broadly reported secondary metabolites	Potential additive or synergistic effects

Table 3 Selected experimental evidence relevant to *C. dactylon* hepatoprotection

Study/model	Plant intervention	Main findings

Devi *et al*. (2017), paracetamol-induced hepatotoxicity in albino rats	Aqueous extract, 200 and 400 mg/kg	Dose-related reduction in SGOT, SGPT and ALP; histological improvement
Singh *et al*. (2009), STZ-associated hepatic injury in rats	Ethanolic extract, 500 mg/kg for 14 days	Reduced SGOT, SGPT and ALP; improved total protein and physiological measures
Mozafari *et al*. (2018), in-vitro phytochemical/antioxidant study	Leaf and rhizome extracts under different drying conditions	Processing altered phytochemical profile and DPPH activity; supports need for extract standardization
Interpretation for rifampicin	No direct equivalence assumed	Evidence establishes plausibility, not proof of rifampicin-specific protection

Table 4 Expected biomarker directions in a rifampicin–*C. dactylon* experimental design

Endpoint	Rifampicin injury	If amelioration is effective
ALT/AST	Increase	Decrease toward control
ALP/bilirubin	Often increase when cholestatic component is present	Decrease toward control
MDA/ROS	Increase	Decrease
GSH/SOD/CAT	Decrease or become impaired	Preservation/increase toward control
TNF-α/IL-1β/IL-6	May increase	Reduction if anti-inflammatory action occurs
Histological injury	Degeneration, vacuolization, inflammation, congestion/necrosis depending on model	Reduced lesion severity

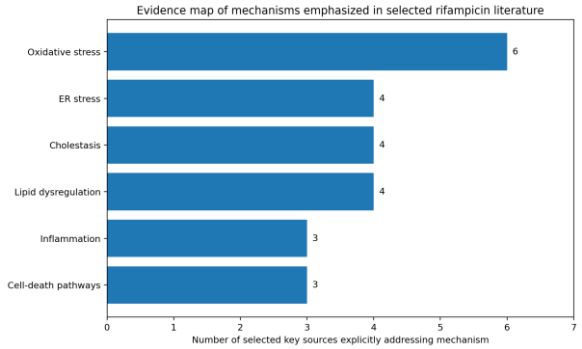

Figure 3. Qualitative evidence map showing how often major mechanisms were explicitly addressed across the selected key rifampicin sources used in this review. Counts reflect the curated review set and are not effect sizes or a meta-analysis.

Table 5. Evidence grading for proposed *C. dactylon* actions against rifampicin toxicity

Proposed action	Evidence level	Rationale
Antioxidant protection	High plausibility	Rifampicin oxidative stress is established; *C. dactylon* antioxidant activity is experimentally supported
Reduction of lipid peroxidation/membrane leakage	High plausibility	Consistent with plant hepatoprotective enzyme and histology data
Anti-inflammatory action	Moderate plausibility	General plant evidence and rifampicin inflammatory involvement overlap
Correction of hepatic lipid dysregulation	Moderate/uncertain	Metabolic effects are reported, but rifampicin-specific PXR/lipid studies are needed
MRP2/FXR protection	Low direct evidence	Important rifampicin mechanism but direct *C. dactylon* validation lacking
Suppression of ER-stress-driven paraptosis	Low direct evidence	Biologically testable hypothesis; currently not demonstrated directly

This article describes two issues related to rifampicin toxicity and its harmful effects on the liver along with several pieces of information confirming the theory of the use of *C. dactylon* for mitigating the adverse effects of this medication. The article structure includes sections that address mechanistic research, animal experiments, articles tackling liver injury caused by antitubercular drugs, and *C. dactylon* research results. Most important findings are peer-reviewed literature that can be accessed in PubMed or any trustworthy academic sources, and some contemporary molecular studies with some improvements in older mechanistic frames. It should be emphasized that the point of the review is not whether *C. dactylon* may help in eliminating the toxic effects of rifampicin. The true point of the review is whether it is possible to say that *C. dactylon* may be used to treat liver injuries stemming from the use of rifampicin. In this regard, the authors made clear the difference because many articles dedicated to the use of herbal medicine demonstrated the potentials of some plants to protect against one or several hepatotoxic agents, while the statement continuously reiterates this position with no reference to any evidence of the other healing effect possibilities. Authors of the article conducted a thorough analysis of the information concerning rifampicin. As a result, the data is classified into groups based on the problems connected with this substance, which include oxidative stress and lipid peroxidation, ER stress and protein balance maintenance, cholestasis and bile outflow, influence of PXR/CYP pathways, and amount of accumulated lipids. As for *C. dactylon*, the information was classified depending on the sphere of research conducted to this plant. This step enabled the authors to develop the model of possible usage of *C. dactylon* for treatment of liver injuries caused by rifampicin. The article also includes the method analysis that reveals the influence of some factors on research results, namely, strain of the animals, the dosage of this substance that was obtained during the experiments as well as the duration of the exposure. There are also three major categories provided in the review. The first category is evidenced by the classification of already established mechanisms. The second category is also concerned with the mechanisms proved experimentally.

Rifampicin: Pharmacology, Metabolism and Clinical Relevance

Rifampicin is designated as a semi-synthetic rifamycin derivative. The drug possesses its antibiotic properties through binding to the beta subunit of bacterial RNA polymerase, which results in the inhibition of the initiation of RNA chains, thus, resulting in stopping transcription in susceptible infections. Rifampicin is of great importance in the treatment of tuberculosis because the drug works as a result of its actions on rapidly reproducing germs and its aiding effects in the sterilization for the long time behavior of any organism.

Rifampicin is administered orally and works from the first minutes of its absorption from the gut and hepatic metabolism in the liver. It has been discovered that different aspects of pharmacokinetics of rifampicin are influenced by food, dose, liver function, and also by autoinduction of the metabolism. One of the positive aspects of this drug is that it induces the metabolizing agents in the body of the human. There is a receptor called PXR. PXR activation leads to the higher amount of mRNAs which is responsible for drug metabolism, but PXR also interferes with the endogenous metabolism of lipids and bile acids. Ezhilarasan has provided the recent results of some studies that show

that the activation of the genes responsible for fatty-acid synthesis begins after using rifampicin in the process. The drug also has some effects on bilirubin excretion. Hyperbilirubinemia may appear due to the action of rifampicin on the liver and bile ducts. Some studies showed that rifampicin causes activation of MRP2 – the transporter named increased activity of this transporter caused the problems of the patients as a result of the increased activity of the transporter. Apart from the information mentioned above about the toxicity of rifampicin, it is important to note that in practice its toxicity or adverse effects are highly linked to the situations, where the drug was used. One should note that steps on animals indicate that the doses given for the drug make its use unacceptable.

Clinical Context and Risk Modifiers of Rifampicin Liver Injury

The hepatotoxicity of rifampicin cannot be viewed in isolation from the factors related to the patient and treatment. The standard regimen of tuberculosis treatment includes rifampicin together with other drugs which may include isoniazid and pyrazinamide during the intensive phase of therapy. Since each of those drugs has its own pharmacokinetic and toxicity profile, the risk of liver injury differs. Hence, the results obtained in animal studies using only rifampicin may hardly be true for the clinical case of DILI.

There are many risk factors. These may include age, nutrition, alcohol use, pre-existing liver disease, hepatitis, and HIV. It should also be kept in mind that an interaction with other drugs may change either rifampicin absorption or absorption of another medicine used simultaneously. Moreover, the process of adaptation may vary from person to person. These factors explain the reasons why some patients have abnormal lab test result while others develop clinical manifestations of hepatitis.

The role of hepatotoxicity goes beyond the simple liver injury. Because if an injury is severe enough to stop treatment, it does mean that there will be no way to treat tuberculosis. The deferral of treatment will lead to worsening of the infectious state of the patient. Thus, the idea of hepatoprotection seems attractive, but it is important that it does not interfere with efficacy of the antimicrobial agent.

There are three types of injury: hepatocellular, cholestatic, or mixed. The elevation of ALT indicates the presence of hepatocellular injury whereas disproportionate elevation of ALP and presence of hyperbilirubinemia indicates cholestatic injury. As rifampicin plays an important role in bilirubin metabolism and bile transportation, the mechanisms of hepatic injury should be investigated.

One of the examples of such investigation is studying the effects of herbal products used as supplements. For instance, the fact that the antioxidant used in animals has an effect on lowering the levels of ALT does not indicate its usefulness unless it influences the metabolism of rifampicin. Similarly, the herbal medicine that influences the values of oxidative markers may have no influence on cholestasis. This explains the importance of studying the level of rifampicin and hepatotoxicity markers in the investigation of *C. dactylon*. Although it has been proved that *C. dactylon* can be used as an adjunct therapy, it cannot be a substitute for rifampicin. The latter is an important drug which cannot be replaced by herbal products. The goal of the study is to find out whether the usage of certain herbal preparation may help to prevent liver injury caused by treatment.

Spectrum of Rifampicin-Induced Toxicity

Rifampicin is the most documented drug concerning toxicity issues, but it has been demonstrated that its effects can extend beyond the liver. Research studies show oxidative stress and inflammatory reactions in kidneys due to the drug, along with the different biochemical changes occurring under the varying duration of exposure and dose. For example, morin-hydrate research conducted on albino Wistar rats showed that after a four-week period of treatment with rifampicin changes in the liver and kidneys, lipid peroxidation processes, depletion of GSH, SOD, catalase, and elevated pro-inflammatory cytokines were observed. Consequently, rifampicin toxicity should be analyzed as a universal process. The liver is revealed to be the most important organ in the context of rifampicin toxicity. The increase in ALT and AST levels demonstrates the presence of liver cell lesions; in its turn, alterations in ALP and bilirubin levels indicate cholestasis. Even if the liver is unable to implement its synthetic functions, total proteins and albumin levels can also show abnormal values. The histological picture may change depending on the severity of the experiment, as it may include the presence of cell degeneration, vacuoles formation, inflammatory infiltration of the tissues, vascular and sinusoidal congestions, centers of necrosis, and so on. Kidneys' alterations are not so apparent in comparison with liver ones, but still play an important role. Oxidative stress can damage renal tubular membranes contributing to decreased glomerular filtration rate and the process of absorption. Therefore, analysis of blood urea and creatinine levels along with the tissue levels of MDA, GSH, SOD, CAT, cytokines, and histology should be carried out for the assessment of drug effects on the other organs. Therefore, systemic blood and physiological changes can arise in the case the organ is damaged. Weight loss, food uptake changes, ratio of fresh organ weight to old organ weight, and hematological parameters are the markers of systemic impacts, even in case of no direct correlation with organ damage. Therefore, both the mode of substance effect and the time of exposure prove to be very important. Early impact can lead to compensatory reactions in one and the same tissue; whereas later impact can lead to either overcompensation or to excess adaptations and/or physiological stresses.

Mechanisms of Rifampicin-Induced Hepatotoxicity

Detoxification is the series of chemical reactions through which reactive oxygen species are neutralized. Throughout the process of metabolism there are always significant amounts of reactive oxygen species (ROS) produced and therefore appropriate concentrations of antioxidative substances (low-molecular weight antioxidants and enzymes) are continuously present. As is evident from many studies, metabolism of drugs leads to the significant increase in ROS production. In cases when ROS production exceeds detoxification processes, biomolecules become prone to oxidation. In rifampicin multihit models, increase in the production of ROS is usually accompanied with decrease in the amount of GSH, SOD, CAT and other substances. It has been established that it is necessary to measure the level of MDA and similar substances.

Endoplasmic-reticulum stress. The endoplasmic reticulum (ER) performs functions of folding proteins, secretion of proteins, maintenance of Ca balance, and important stages of lipid formation. When there occurs accumulation of unfolded proteins, this induces the process called UPR, which at the beginning is the regulatory process where normal protein synthesis is inhibited, and lots of chaperones are produced. If the process lasts for a sufficiently long time, the UPR will result in the death signal eventually.According to the research carried out in 2023 based on rifampicin-induced toxicity, there was some elevation in the stress markers such as BiP, CHOP, and polyubiquitinated proteins which were accompanied by a high-level of vacuolarization in the cytoplasm and decrease of the autophagy process. This means that cell death is similar to paraptosis due to endoplasmic reticulum stress.

Cholestasis and biliary excretion. Rifampicin is inhibiting bile salts and bilirubin transport. Zhuang *et al*. (2022) revealed that cholestasis is one of the main features of rifampicin-induced liver injury. Experimental studies related to the MRP2 protein revealed that rifampicin decreases levels of canalicular transporters, which leads to accumulation of conjugated bilirubin inside cells. Experimental studies showed that 4-phenylbutyrate is capable of decreasing rifampicin-induced endoplasmic reticulum stress and ubiquitination of MRP2 thus providing much easier management of bilirubin. The relationship between endoplasmic reticulum stress and cholestasis is one of the examples of toxic pathways interaction.

PXR, CYP regulation, and fat accumulation. Rifampicin is a strong PXR activator. PXR regulates transporters and enzymes but also has some roles in regulating different metabolic processes that influence the storage and absorption of fats. The usage of rifampicin was associated with enhanced activity of perilipin-2, the activation of PPAR-gamma signaling, and CD36 which led to fat accumulation in the liver. The burden of fat may make the organism more susceptible to oxidative and inflammatory impacts.KLF15 mediated modulation of Cyp3a11 is critical for rifampicin toxicity in mice (Hou *et al*. 2024). These developments also confirm that the perception of foreign substances, drug metabolism in the organism, and energy metabolism processes are interrelated.

Inflammation- Damage to liver cells results in the production of danger signals that serve as signals for Kupffer cells which, in their turn, attract immune cells to the site of inflammation. When danger signals appear, a cascade of events starts, which can lead to further liver damage and production of reactive oxygen species. In the recent research on rifampicin-induced hepatotoxicity using single-cell and proteomic approaches, macrophages appeared, and this correlated with the worsened state of liver cells. This contradicts earlier

assumptions about the use of herbal approaches since flavonoids and phenolic compounds are known as molecules that have antioxidant and preventative properties concerning the modulation of inflammatory pathways.

Autophagy and death of cells. Autophagy is a process that helps get rid of damaged proteins and organelles. The inhibition of autophagy at the moment of severe endoplasmic reticulum (ER) stress may cause accumulation of damaged particles. Rifampicin-induced inhibition of autophagy takes place along with the generation of ROS. Other combinations of anti-tubercular drugs may affect Bax/Bcl-2 ratio, mitochondrial membrane potential, cytochrome-c release, and apoptosis. Therefore, a precise prevailing mechanism of cell death may depend on dose, drug combination, species, and the methodology of research.

Interaction of various mechanisms. The oxidative stress can lead to the destruction of ER; at the same time, ER stress leads to the disturbance of calcium homeostasis and ROS generation; cholestasis facilitates exposure of liver cells to toxic bile acids; accumulation of lipids raises the risks of peroxidation; inflammation boosts ROS generation; and impaired autophagy leads to prolonged ER stress. The network model can be considered especially after the lecture on *C. dactylon* since a multi-component preparation based on this plant may have low impact on several targets rather than high effect on only one.

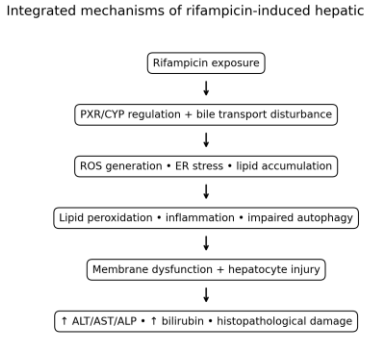

Figure 1 Integrated conceptual pathway of rifampicin-induced hepatic injury based on the reviewed mechanistic literature.

***Cynodon dactylon*: Botanical Profile and Traditional Relevance**

Cynodon dactylon (L.) Pers. is a type of grass belonging to the family Poaceae. It grows by means of stolons and rhizomes and is resistant to environmental stress and repeated cutting. The plant is found in the tropical and warm temperate areas and is often considered a weed in agronomy. Nevertheless, it has a long history of ethnomedicinal use in South Asia and other areas.

The Indian natives call it Durva, Doob, Dub, and other regional names. Traditionally, it has been prepared in the form of fresh juice, paste, powder, and decoction. Pharmacognostic studies claim to find it useful for treatment of wounds, bleeding, urinary diseases, diarrhea, inflammation, and disorders related to metabolism. Though it is not an equivalent of the clinical proof, they have provided guidelines for carrying out the pharmacological screening.

The plant is attractive from the experimental perspective since it is available widely and is cheap. Different types of whole-plant preparations used such as leaves, aerial, roots, and rhizome. Such diversity has caused the standardization issues since an aqueous extract of fresh aerial tissue can be qualitatively and quantitatively different from ethanolic extract of rhizome. Besides that, different factors such as country of origin, soil, season, drying temperature, storage process, and extraction time affect the metabolite content of the plant. Mozafari *et al*. (2018) pointed out that the method and temperature of drying have impact on the phytochemical composition and antioxidant potential of *C. dactylon* leaves and rhizomes, which resulted in discovery of constituents like fatty-acid derivatives, phytol, and many others as well as varying antioxidant properties. This result has a significant implications for the hepatoprotection research as the biological effect cannot be attributed to the *C. dactylon* unless the plant material and its processing methods are described in detail. Recent reviews talk about importance of standardization. For instance, Verma (2025) described flavonoids, which are also important in the understanding of the plant's properties, such as apigenin, luteolin, and vitexin, together with terpenoids and other constituents. Earlier reviews by Ashokkumar *et al* (2013) and Shendye and Gurav (2014) confirmed importance of flavonoids, carotenoids, alkaloids, glycosides, proteins, and organisms similar to triterpenoids in the efficacy of the plant.

Phytochemistry and Antioxidant Potential of *C. dactylon*

Among the most significant phytochemical groups involved in the examination of oxidative injury caused by drugs are phenolic substances and flavonoids. Their effectiveness has been attributed to their ability to provide hydrogen ions and electrons to free radicals and to block the reactions that initiate the lipid peroxidation process. Besides, flavonoids may influence intracellular signaling as well as taking part in the expression of antioxidant genes, the activity of inflammation-inducing transcription factors, and altering the nature of membranes.

The plant named *C. dactylon* has both the primary and secondary metabolites. Therefore, different sources identify such flavonoids, carotenoids, alkaloids, glycosides, terpenoids, the triterpenoid class of chemicals, saponins, phenolic acids, proteins, sugars, and mineral substances. Other more specialized works have highlighted phytol and compounds derived from fatty acids being present in and extracted from leaves and rhizomes. More recent reviews of the literature underscore apigenin, luteolin, and vitexin. The significance of these components lies in the fact that analogous flavonoids have been proven to function as antioxidants and hepatoprotectants.

Many types of antioxidants have been investigated using chemical tests like DPPH scavenging test or ferric reducing capacity test. For instance, Mozafari *et al*. (2018) demonstrated strong DPPH quenching activity in some preparations made of dried leaves and rhizomes and showed how processing affected such activity. Other investigations involving medicinal grasses have shown reducing capacity of entire plants *C. dactylon*, which confirms the possibility of claiming redox reactivity but does not mention bioavailability or efficacy in the liver.

In vivo, testing antioxidant capacity should usually be based on the investigation of the state of the organs. If an extract helps to protect the liver effectively, there should be some way of keeping the levels of the GSH or SOD intact while also decreasing the number of MDA or ROS. Previous experiments have demonstrated some information regarding antioxidant activity in the liver connected with *C. dactylon.* However, it still remains vague what substances discovered in this plant may be responsible for such effect. The problem of bioavailability remains unresolved. Even though a substance has strong DPPH scavenging effect in vitro, it may be poorly absorbed or destroyed. Conversely, even though a metabolite does not possess high scavenging activities, it may activate internal antioxidant activity. Therefore, it would be wise to carry out the research based on phytochemical profile of the plant combined with pharmacokinetic data and molecular markers rather than rely solely on chemical assays.

Experimental Evidence for Hepatoprotective Activity of *C. dactylon*- The literature regarding the hepatoprotective effects of *C. dactylon* covers several chemical models of liver damage. These models, although not necessarily confirming protection against rifampicin, show how particular extracts may change different liver biochemistry and histology. The study of Devi and colleagues (2017) showed the effect of an aqueous extract of *C. dactylon* on paracetamol-induced liver damage in albino rats. The extracts of two doses (200 and 400 mg/kg of body weight) gave lower levels of SGOT, SGPT, and ALP than what was expected in the case of liver damage. The higher dose showed a rather strong effect, which was nearly comparable to N-acetylcysteine effect. The results of the histological analysis were supportive of the received biochemical data with milder liver necrosis, congestion, and portal-tract infiltration after an extract administration. Singh and colleagues (2009) explored the effect of alcoholic extract of *C. dactylon* on streptozotocin-induced diabetic rats with liver damage. Two weeks of treatment with the extract in the dose of 500 mg/kg allowed overcoming the liver damage. The findings of the research were positive; however, the toxic mechanism differs from the one caused by rifampicin. Previous studies have indicated protection against carbon tetrachloride and other hepatotoxic agents. In these studies, the positive results were attributed to stabilization of membranes and antioxidant action. Since the quality of such researches varies, these findings should be taken merely as confirmatory evidence.

C. dactylon evidence is strong because it is confirmed in multiple types of liver damages. However, it is weak because it has rather high

degree of inconsistency due to variability in the type of extract used, part of the plant, dose, duration of administration, type of toxicant, and number of toxicological indicators. Some of the studies are rather small, but there also numerous conference abstracts presented, and only few of them utilize modern techniques of molecular biology.

Proposed Mechanisms of Amelioration Against Rifampicin Toxicity- The protective possibilities of *C. dactylon* against the harmful effects of rifampicin are formulated in the plate of multiple mechanisms that are based on commonalities between the kinds of damages caused by rifampicin and the properties of plants. 8.1 Reduction of oxidative stress. The most direct approach may be that phenolic and flavonoid compounds can lower the ROS levels. This could be achieved by direct scavenging of radicals, chelation of metals, preventing lipid peroxidation chain reactions, or by triggering the production of the internal antioxidants. In a rifampicin model, antioxidant action is expected to reduce the levels of MDA and ROS as well as to retain GSH, SOD, CAT, and glutathione peroxidase.

Stabilization of membranes- The attack on phospholipids by oxidants destroys membranes of hepatocytes. If *C. dactylon* can lower lipid peroxidation, the function of membranes of hepatocytes will improve, and the levels of ALT/AST in blood will decrease.

Anti-inflammatory effect- Flavonoids and phenolic compounds can influence inflammation processes in all biological systems. If *C. dactylon* can lower the activation of NF-kappaB pathways or reduce the levels of TNF-alpha, IL-1beta, and IL-6, the link between inflammation and ROS can be broken.

Modulation of ER stress- There is currently no solid evidence that *C. dactylon* affects rifampicin-induced signaling via BiP, CHOP, or UPR pathways. Nevertheless, a decrease in oxidative stress may lead to a reduction in the pressure on protein folding and disturbances in the endoplasmic reticulum.

Normalization of bile transport as rifampicin is known to impair the function of MRP2, the protective mechanism that would qualify as complete must include normalization of bilirubin concentration and functioning of canalicular transport proteins.

Metabolism of lipids PXR activation by rifampicin may lead to accumulation of lipids in the liver. Some studies show that *C. dactylon* has been successful in reducing lipids; therefore, it may help against steatosis, but there is currently no confirmed evidence of effects on PXR CD36, PPAR-gamma, perilipin-2, or fatty acid oxidation in the case of rifampicin treatment.

Cytoprotection and histology preservation- The combined effect of antioxidant action, anti-inflammatory effect, and stabilization of membranes may prevent the development of degeneration and necrosis in liver cells.

Biomarkers and Experimental Endpoints- An intensive study of rifampicin-C. dactylon should involve performance of biochemical and oxidative and inflammatory and molecular and histological evaluation points. ALT and AST serums act as important markers of liver damage.

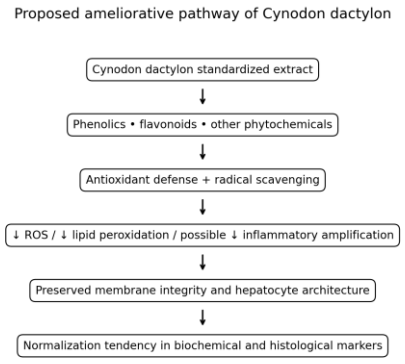

Figure 2 Proposed ameliorative pathway of *C. dactylon*. Direct antioxidant and hepatoprotective evidence is stronger than evidence for rifampicin-specific molecular targets.

ALP and gamma-glutamyl transferase (if possible) as well as bilirubin coefficients help to assess cholestatic component involvement. The data about protein, albumin, and globulin will bring the additional information about liver synthetic and general reactions of this organ. The redox status of the tissue should involve MDA or any other product of lipid peroxidation, GSH, superoxide dismutase and catalase hoping about the availability of glutathione peroxidase. It is possible to supplement the data by performing direct tests with ROS while making sure that proper controls are being used. Since oxidative evaluations are very sensitive to the process of tissue manipulation, collection and storing of samples must be standardized. The evaluation should involve various cytokines like TNF-alpha, IL-1beta, IL-6, at some times it is possible to use immunohistochemical or messenger RNA investigation on macrophage activation. This is especially important as the latest discoveries in the field suggest involvement of the patients' macrocytes after usage of rifampicin. Another ER-stress parameter can be BiP/GRP78, CHOP, PERK, phosphorylated eIF2alpha, ATF4 and polyubiquitinated proteins that should be utilized to evaluate autophagic flux (using LC3-II, p62 or respective markers) and cell-death mechanism (through caspases, Bax/Bcl-2, necroptosis, morphological features of paraptosis-like process). Bile transport can be evaluated through parameters like MRP2, BSEP, FXR-related pathways and encoding of serum bilirubin. Lipid metabolism can be assessed through determination of lipid levels in the liver, Oil Red O staining, CD36, PPAR-gamma, perilipin-2 and genes encoding fatty-acid oxidation. It is necessary that the above-mentioned parameters are evaluated in a modern way. Histopathology should not just provide qualitative evaluation but also involve scoring as well. The following points can be taken into account: the degenerative process in the liver, liver necrosis, inflammatory process in tissues, the presence of liver-stenosis.

Evidence Synthesis: Rifampicin Injury Versus *C. dactylon* Protection- The evidence can be visualized as a mechanism-countermeasure matrix. It has been shown that rifampicin is related to oxidative stress, endoplasmic reticulum stress, cholestasis and lipid metabolism alterations, inflammation, and cell death. In contrast to that, *C. dactylon* has stronger experimental evidence demonstrating its antioxidant activity, normalizing of enzymes, tissue protection, as well as some anti-inflammatory and metabolic effects. The coincidence between the two aspects is the strongest in terms of oxidative stress and least significant for the role of rifampicin transporters or the way of ER stress signaling regulation. The asymmetry plays an important role in science as it implies that antioxidant and general hepatoprotective effects are the best reason to study *C. dactylon* while statements regarding PXR, MRP2, FXR, and/or paraptosis remain assumptions for now. Review papers usually lack accuracy when they say that everything known about a plant can be attributed to each and every mechanism of a toxic agent making the focus of the paper less effective. It is more reasonable to rank the mechanisms based on evidence available. In particular, high plausibility mechanisms include antioxidant protection, preventing lipid peroxidation, stabilization of membrane and preventing enzymes from getting out of cells. Moderate plausibility mechanisms include anti-inflammatory and metabolic modulation activities, which have been supported by evidence but not necessarily in models on rifampicin. The least plausible mechanisms include such properties as specific protection of MRP2, normalization of FXR and PXR signaling, and inhibition of paraptosis. Another relevant aspect is organ specificity. Being the most extensively studied organ in connection with both rifampicin and *C. dactylon* research, liver protection seems to be the most reliable in terms of mechanism issues. Providing some information about the possibility of kidney protection is possible, but still, there is no certified evidence for that. The same refers to blood protection: though it may seem reasonable, nothing can be proven for now.

Safety, Dose Standardization and Herb–Drug Interaction Concerns- *C. dactylon*'s designation as a natural or traditional remedy does not necessarily mean that it is safe for patients on rifampicin therapy. Herbal products may consist of many substances that can either impact drug absorption, metabolism, transport, or elimination. This is of particular concern with rifampicin given that this drug is a potent enzyme and transporter inducer and tuberculosis therapy consists of the use of various substances with a narrow therapeutic range. Research on *C. dactylon* in experimental animals has involved the use of a wide variety of doses. For instance, dosages of aqueous extract equal to 200 or 400 mg/kg have been used in studies on paracetamol-induced liver injury, while the administration of the ethanolic extract of *C. dactylon* in a diabetic rat models has involved doses equal to 500 mg/kg. The dosages used in animal studies cannot directly be translated into clinical recommendations

since exposure to the extract can vary according to extract yield, composition, route of administration, and duration of exposure. A standardized extract should provide detailed information regarding the plant part that has been used, botanical identification, voucher information, type of solvent used, extraction rate, amount of extract that has been obtained, and important chemical markers that were identified and the tests conducted for the purpose of detecting contamination. Acute toxicity should not be the only measure. Safety after multiple doses should be assessed since rifampicin administration is long-lasting. Future studies on *C. dactylon* should include hematological and kidney function tests, liver function tests, and monitoring body weight in animals administered the extract. If the product is going to be produced long-term, testing for genotoxicity and reproductive toxicity may also be useful. Herb-drug interaction studies are necessary before the clinical application of the extract that contains *C. dactylon*. The reason is that rifampicin induces PXR activation and induction of CYP enzymes; therefore, any extract constituent that either locks this activity or induces it even more will impact either the extent of rifampicin action or the action of antitubercular agents given with this drug. There might be a protective effect but it could be counterbalanced by the lower action of the antibacterial agent.

When evaluating the extracts used as adjunctive agents, microbiological effectiveness should also be taken into consideration. An ideal translational program should start with assessing safety and chemistry of the agent used before moving on to investigating pharmacokinetic interactions and effectiveness of the extract after which controlled clinical trials should be conducted.

Research Gaps and Future Directions- The notable gap identified in research relates to the lack of direct studies testing *C. dactylon* against the toxicity induced by rifampicin. While current hepatoprotective research shows that the idea is plausible, it is not enough for drug-specific validations to take place. A high-caliber study must implement an injury protocol for rifampicin that meets validation conditions, a sufficient number of samples, random allocation of groups, blind evaluation of outcomes, established main endpoints, and transparent statistical analyses. Standardization for plant material is also important. Future research must explore the difference between the aqueous and hydroalcoholic extracts only if their phytochemical composition is known. HPLC or LC-MS fingerprints make it possible to detect the marker compounds that can provide the plant material's consistency across batches. The total content of phenolic compounds and flavonoids can be viewed as auxiliary indicators. The analysis of dose and response must also take place. Instead of taking only one previously tested dose or dose used in traditional medicine, researchers need to try two or three doses. Moreover, the extract must be tested separately. Therefore, it would become possible to determine the smallest dose that provides an effect, the best result that can be achieved, and the possible damage that high doses can cause. Positive controls, e.g. silymarin and N-acetylcysteine, can probably be used depending on the type of injury. Mechanistic studies must also go beyond the serum enzymes. In addition to these measurements, PXR/CYP3A, KLF15, MRP2, FXR, CD36, PPAR-gamma, perilipin-2, ER stress markers, antioxidants, as well as indicators of the death of cells must be included in the design. While the studies do not have to analyze all of these markers, the choice of endpoints must aim at testing a given hypothesized mechanism. Omics approaches create additional opportunities. For example, transcriptomics helps detect those gene networks that change because of rifampicin and are restored with the help of *C. dactylon*. Proteomics shows changes in enzymes, transporters, and other stress proteins, while metabolomics gives information about the composition of bile acids, lipids, and redox metabolites. All these outcomes can help develop pathways and biomarkers for further research. Furthermore, isolating the active constituents is also significant. Bioassay-guided isolation can establish whether the protective effect is due to certain flavonoid or phenolic compounds or due to synergy between different phytochemicals. Once the active fractions are found, the process of pharmacokinetics and distribution in cells can begin. Eventually, one must note that there should be no rush in the process of translating the obtained results into clinical cases. Before telling about the possible interactions of *C. dactylon* with rifampicin, researchers must conduct pertinent studies proving that interactions between them do not prevent rifampicin from having an effect in the treatment of tuberculosis.

Conclusion

Rifampicin is essential in management of tuberculosis; however, its role in inducing of liver injury is complex and important clinically. At present time, it is hypothesized that the pathogenesis of rifampicin-induced hepatotoxic reactions involves a large set of processes, such as activation of xenobiotic receptors and oxidative stress, as well as induction of endoplasmic reticulum stress, cholestasis, accumulation of lipids, etc. Recent studies have refined this model by describing involvement of KLF15-Cyp3a11 regulation, recruitment of specifically macrophages, suppression of antioxidant genes, and instability of MRP2. *Cynodon dactylon* appears to be a widely known grass with a rich phytochemical profile and considerable evidence of antioxidant action and hepatoprotective effects in some experimental models. More particularly, a lot of studies have been reported on the action of its aqueous or ethanol extracts, which reduce liver enzymes and improve histological outcomes of paracetamol- and streptozotocin-induced liver injuries in rats. All the above points to the validity of the research on the grass in terms of potential reduction of toxic effects of rifampicin. The most prominent mechanism is the reduction of oxidative stress, enhancement of antioxidant mechanism, suppression of lipid peroxidation, stabilization of cellular membranes, as well as other clinically relevant effects of the grass. Direct participation of *C. dactylon* extracts in any specific pathways that are triggered only by rifampicin like activation of PXR, MRP2, FXR, and ER-stress signaling are still unclear. Thus, now it is possible to say that *C. dactylon* can be regarded as a good experimental source of phytochemicals possessing hepatoprotective properties but not as a widely used clinical antidote. The development into the direction of the creation of any therapeutic product based on the plant will require the standardization of the extracts, evaluation of dose-response relations, testing safety of the product in patients and clinical studies.

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